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Trophoblast Organoids: A New Tool for Studying Placental Development

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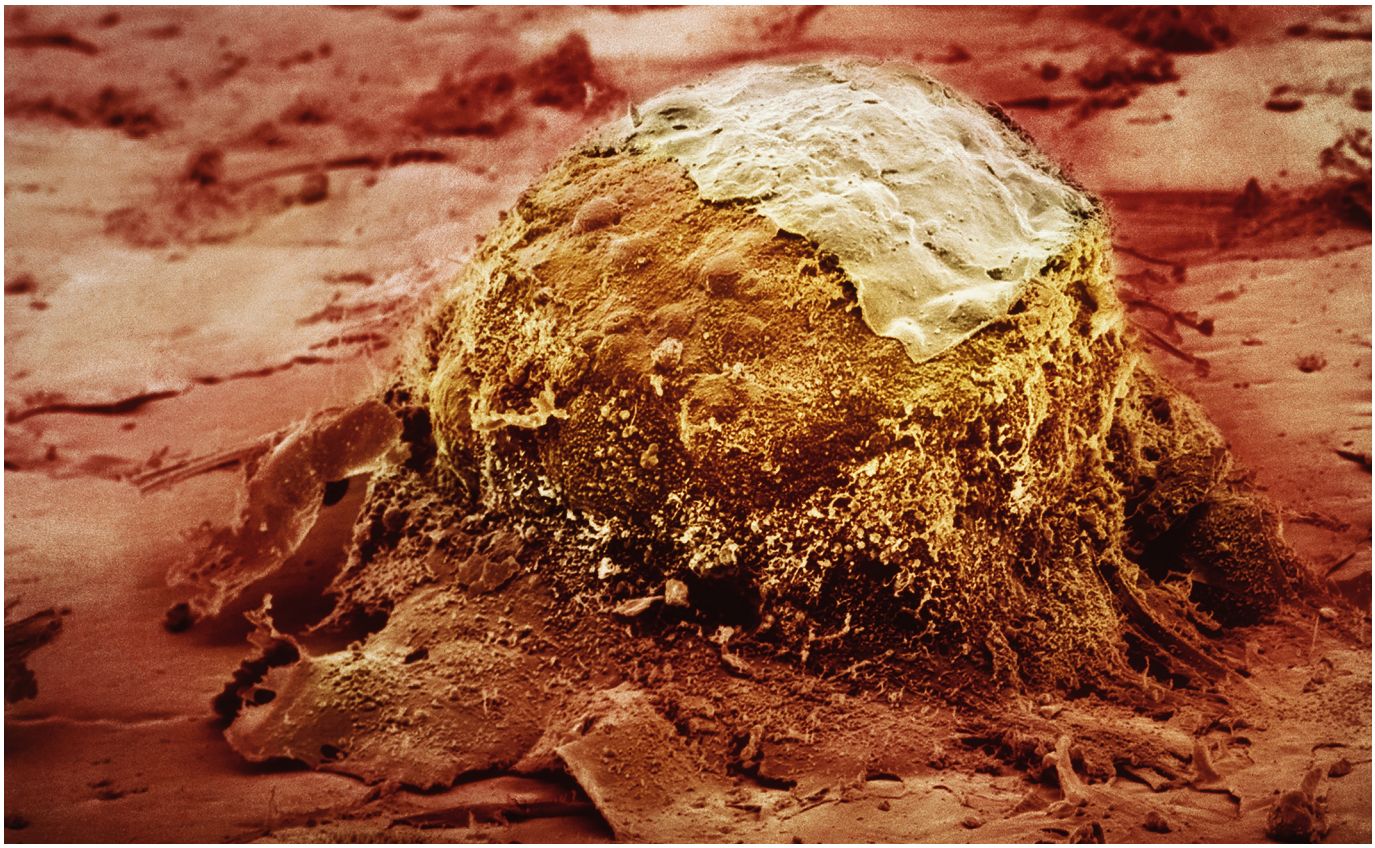
Adverse pregnancy outcomes such as implantation failure, fetal growth restriction, preeclampsia, and stillbirth occur worldwide at concerning rates.[1–4] Although their root causes are yet to be fully elucidated, the majority of these outcomes can be traced back to defects in placenta formation,[5] a process that is still poorly understood. A new report in *Environmental Health Perspectives* leveraged a novel *in vitro* model to examine how organophosphate flame retardants (OPFRs) placentation and associated effects on birth outcomes.[6]

In humans, the process of placentation begins very early in pregnancy, when embryonic cells called trophoblasts enter the uterine lining in a process called invasion. There, they fuse fetal and maternal tissue.[7] The placenta continues to develop throughout the first trimester, acting as a vital interface that regulates nutrient exchange and waste removal, protects against external insults, and secretes hormones that maintain pregnancy and prepare the mother's body for birth.[8]

Growing evidence suggests that environmental exposures may contribute to pregnancy complications that are mediated by disruption of placentation.[9–11] The effects of these complications can endure into adulthood,[12] making the identification of such environmental culprits all the more pressing. Epidemiological studies have linked OPFRs—widely used in furniture, textiles, electronics, building materials, and food packaging[13,14]—to these adverse pregnancy outcomes.[15]

Despite the varied and important roles of the placenta in fetal development, current knowledge about human placentation and how environmental chemicals may influence the process has been hampered by limited access to developing tissues and the absence of representative experimental models.[16] "To address these conundrums, our study applied human trophoblast organoids, which can display near-physiological cellular composition and behavior relative to immature human placenta," says senior author Jianying Hu, a professor in the Department of Environmental Science at Peking University.

Organoids are self-organizing, three-dimensional structures typically derived from stem cells or tissues in culture that can recapitulate the complex structural, biological, and functional features of tissues and organs, bridging the gap between *in vitro* and *in vivo* models.[17,18] In the present study, Hu and colleagues cultured trophoblast organoids from placental villi donated by five women.[6] They used the organoids to screen the placental toxicity of 46 OPFRs. Three of those chemicals were determined to affect cell proliferation without impairing cell survival. One of the three, 2-ethylhexyl diphenyl phosphate (EHDPP), has been widely detected in both environmental and human samples[11,19]



Colored scanning electron micrograph of a human embryo at 11 days implanted in the wall of the uterus. New rodent and *in vitro* experiments suggest that chemical exposures may interfere with implantation. Image: © Lennart Nilsson, TT/Science Photo Library.

and is associated with pregnancy complications.[20,21] The authors wrote that "EHDPP is the only organophosphate ester approved by the U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition for use as a fire retardant in food packaging materials."[6]

In subsequent in-depth mechanistic studies, they showed that EHDPP reduced metabolic function of trophoblasts. These results were closely recapitulated in parallel *in vivo* mouse experiments, using doses comparable to human exposures. Both immature and mature placentas from mice exposed before and during gestation exhibited decreased metabolic function and cell proliferation, compared with controls. Finally, exposure to EHDPP led to increased implantation failure, fetal growth restriction, and stillbirth. In offspring that survived to adulthood, exposure was also linked to impaired glucose tolerance, a sign of prediabetes.

"The authors were able to use a combination of tools to screen the toxicity of numerous compounds and also validated these results in an *in vivo* model," says Liping Feng, an associate professor at Duke University School of Medicine, underscoring the reliability of the study. "In addition, they measured concentrations of EHDPP in the placenta, which is very important because it can differ from that of the maternal circulation."

Feng, who was not involved in the study, adds that it is important to look beyond placental mechanisms to evaluate whether OPFRs can directly affect the embryo or fetus. Toxic chemicals can cross the placenta and even accumulate in the embryo.[22–24] One recent study[25] detected OPFRs in both the maternal and fetal sides of the placenta, highlighting the need to fully characterize their mechanism of action to better inform exposure reduction policies.

Almudena Veiga-Lopez, an associate professor at the University of Illinois at Chicago College of Medicine, notes that this study primarily focuses on proliferation, which is a feature of "stemness" shared with cell types in other organs. Veiga-Lopez, who also was not involved in the study, says future studies should focus on evaluating functions specific to placental cells, such as cell invasion, cell fusion, and steroidogenesis.

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